

GlaxoWellcome

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Dockets Management Branch
HFA-305
Food and Drug Administration
5600 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry: Clinical Considerations for Accelerated and Traditional Approval of Antiretroviral Drugs Using Plasma HIV RNA Measurements
***Federal Register* 64: 47844-47845 (September 1, 1999)**
[Docket No. 99D-2445]
Comments for Consideration

Dear Sir or Madam:

Reference is made to FDA's issuance of a draft guidance for industry entitled *Clinical Considerations for Accelerated and Traditional Approval of Antiretroviral Drugs Using Plasma HIV RNA Measurements*. The purpose of this letter is to provide written comments on this draft guidance.

Glaxo Wellcome, a research based company, has been an industry leader in the development of new drugs to treat HIV infection. We currently have 5 approved drugs on the market for treatment of HIV infection: Retrovir® (zidovudine), Epivir® (lamivudine), Combivir® lamivudine/zidovudine), Ziagen® (abacavir sulfate) and Agenerase™ (amprenavir). Glaxo Wellcome is committed to continued research and development of new drugs in the fight against human immunodeficiency virus infections. We have drawn on our extensive experience in preparing these comments. Our remarks are grouped according to section headings appearing in the draft guidance.

Section II. Background

In this section, the draft guidance notes the "successes of combination therapy and subsequent decline of HIV-related clinical illnesses." To further support this statement, it would be helpful to add 1-2 key citations about the major decline in HIV-related illnesses since introduction of HAART. Our suggestion for one key citation is as follows:

- Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N *Engl J Med* 338: 853-860 (1998).

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This section refers to the work of the Surrogate Marker Collaborative Group. Readers would benefit from inclusion of the following citations, which carefully chronicle this work:

- Murray JS, Elashoff MR, Iacono-Connors LC, Cvetkovich TA, Struble KA. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS* 13: 797-804 (1999).
- Chuang-Stein C, DeMasi R. Surrogate endpoints in AIDS drug development: current status. *Drug information Journal* 32: 439-448 (1998).

In addition, the following publication reports on a meta-analysis of 15 controlled clinical trials supporting the use of both CD₄ cell count and plasma HIV RNA as endpoints of antiretroviral therapy:

- Hill AM, DeMasi R, Dawson D. Meta-analysis of antiretroviral effects on HIV-1 RNA, CD₄ cell count and progression to AIDS or death. *Antiviral Therapy* 3: 139-145 (1998).

We recommend inclusion of the various references in order to clearly identify the specific scientific bases for key aspects of the draft guidance. This will improve the final guidance and facilitate future efforts to revise and update the guidance.

Section III. Accelerated Approval

2nd paragraph:

This guidance suggests that a factorial design could be employed in a study for accelerated approval, yet the requirement that the treatment effect of each drug of interest be isolated argues strongly against the use of a factorial treatment assignment. It would be helpful to include an example. To our knowledge, the factorial design has not been used reliably or extensively in clinical studies of antiretroviral drugs.

3rd paragraph:

Please clarify the meaning of the statement, “*In addition to demonstrating a drug’s safety and efficacy in patients with limited options...*”. This statement implies that every NDA for a drug seeking accelerated approval must demonstrate safety and efficacy in patients with limited treatment options. We believe this statement should be modified for two reasons. First, the INDICATIONS sought for the drug is a decision by the sponsor based predominantly on the pharmacologic properties of the drug. It is conceivable, and indeed foreseeable, that use in a patient population with limited treatment options will not be pursued by the sponsor for certain drugs, given that (1) some drugs may have a pharmacologic profile not suitable for such patients or (2) the sponsor may prefer first to establish safety and efficacy of the drug in patients with less advanced disease. Historically, these approaches have been acceptable options and they should remain acceptable options for the future. Such options, in and of themselves, are not inconsistent in any way with the Subpart H regulations.

As the number of drugs on the market to treat HIV increases, it will become more difficult to identify new drugs that meet an unmet medical need. We applaud the Division for including in the draft guidance a list of criteria that could qualify a drug for accelerated approval.

Section III.A. Safety

1st paragraph:

Throughout the period 1995- 1999, the DAVDP's guidance to sponsors has been that the original NDA should provide safety data on 400 to 500 patients with 6 months treatment with the proposed commercial dosage regimen. We continue to support this guidance for safety data in an initial application for multiple reasons:

- The emphasis in the draft guidance on studying antiretroviral agents in more advanced patients who have limited treatment options, will make it difficult to obtain safety data on more than 400-500 patients for six months.
- Safety data in more advanced patients will be difficult, if not impossible, to collect in a manner enabling a quantitative comparison of the investigational regimen versus a standardized control. This difficulty in using a standardized control will greatly impair premarketing efforts to understand any unique safety issues associated with the investigational drug.
- In addition, a substantial proportion of sponsors' safety databases for antiretroviral drugs in the past has been derived from expanded access programs. As the need for expanded access becomes more focused, this will reduce the amount of safety data available for inclusion in initial applications.

In the draft guidance, reference to the ICH *Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long Term Treatment of Non-Life-Threatening Conditions*, is somewhat confusing in that it wrongly suggests that it is applicable to antiretroviral drugs. A more appropriate guidance to reference would be the European Union guidance on antiretroviral drugs. [Points to Consider in the Assessment of Anti-HIV Medicinal Products, September 1997]. This EU guidance represents the thinking of another major group of health regulatory authorities and is entirely consistent with the prior guidance from DAVDP that safety data on a total of 300 - 600 patients with 6 months treatment with the proposed commercial dosage regimen is sufficient for inclusion in the original NDA.

Section III.B. Efficacy

2. Control Arms:

This section states that “control regimens regarded as suboptimal or nonpreferred may be considered unethical and may jeopardize the viability of a study”. We urge you to change

the word “regarded” to “proven”; we also urge you to delete the word “nonpreferred.” The design and conduct of clinical trials must be guided by concrete data rather than subjective belief. We all recognize the challenges of designing clinical trials and selecting an appropriate control regimen, consistent with the objectives of the trial. It is important not to further compound these challenges by excluding certain potential control regimens without reliable data showing that they are suboptimal. Moreover, whether a control regimen is preferred or nonpreferred is for patients and prescribers to consider and this factor will impact the pace of enrollment, not the validity of the design.

We also suggest that current DHHS and IAS treatment guidelines be cited in FDA’s draft guidance as a source of guidance for sponsors on the selection of an appropriate control regimen (based on the state-of-art treatment regimens).

3. Study Design Options

Under Equivalence Trial Designs, the draft guidance states that *“it is important that the contribution of the substituted drug to a regimen’s overall activity be previously characterized in the population of interest.”* In an equivalence or non-inferiority trial, it is imperative that the control (i.e., the component of the standard regimen which is serving as the control), rather than the test, be previously characterized in the population of interest. We suggest that this should read, *“it is important that the contribution to a regimen’s overall activity of the control drug (i.e., the component of the standard regimen for which the test drug will be substituted) has been previously characterized in the population of interest.”*

In the statistical literature, an “equivalence” trial is one that seeks to demonstrate that neither treatment arm is clinically significantly different from the other, while a “non-inferiority” trial is one that seeks to demonstrate that one treatment arm is not clinically significantly worse than the other arm. In the context of this guidance document, it would be more descriptive to use the term “non-inferiority.”

Under Dose Comparison Trial Designs, we propose this section be revised to the following, *“Dose comparison studies can support accelerated approval, and such studies should be discussed with the Division in advance.”*

5. Study Endpoints

The draft guidance addresses accepted approaches to analysis of plasma HIV RNA data (i.e., proportion of patients with values below limit of detection and mean change from baseline over time). FDA should consider citing other measures that may be useful such as average area under plasma HIV RNA curve over time minus baseline; and time to virologic failure. The guidance should also state a willingness to embrace other valid ways to analyze data as they emerge over time (e.g., viral dynamics, resistance evaluations).

Also, since this draft guidance encourages studies in patients with advanced HIV, FDA should reiterate its historical willingness to grant labeling based on endpoints that are unique to such patients. These endpoints include the 10: 10 endpoint (proportion of patients

achieving a 10-cell CD₄ increase over baseline or a 10% increase in CD₄ cell count over baseline).

The second paragraph states, *“However, mean changes in HIV RNA from baseline over time may be another useful analysis for heavily pretreated patient populations in which reduction in HIV RNA is apparent, but in which few have achieved responses below the assay limit.”* Our research confirms that this often is a typical response in patients who have been heavily pretreated. We agree with FDA that it is appropriate to consider this type of analysis in this patient population.

6. Statistical Considerations

It is helpful for the draft guidance to suggest that sample size be calculated to provide an appropriate confidence band of equivalence of the regimens being compared. However, the draft guidance gives an instruction that, to our knowledge, has not been applied in clinical drug development to date for the 16 FDA-approved antiretroviral drugs. To be specific, the draft guidance recommends calculating sample size based on a delta of 10%. Operationally to date, most sample size calculations have been made with a delta of 12% and we suggest that the experience to-date supports the adequacy of the 12% non-inferiority delta in most cases. Nonetheless, we recommend that the draft guidance describe 12% as one example, while also stating FDA’s openness to consider alternatives for specific studies based on appropriate rationale.

The table below presents total sample sizes needed for a two-arm trial (80% power) for a variety of common success rates and non-inferiority deltas. The wide range of required sample sizes demonstrates the significant impact of the delta.

| Common Success Rates | Non-inferiority Delta | | | |
|----------------------|-----------------------|------|------|------|
| | 0.15 | 0.12 | 0.10 | 0.08 |
| 0.50 | 350 | 546 | 786 | 1228 |
| 0.60 | 336 | 524 | 754 | 1178 |
| 0.70 | 294 | 458 | 660 | 1032 |
| 0.80 | 224 | 350 | 504 | 786 |

The statement that “both equivalence and superiority can be assessed in the same study” is welcome but conflicts with previous practice. We suggest incorporating the following text (taken with minor modification from the draft *“Points to consider in biostatistical/methodological issues arising from recent CPMP discussions on licensing applications: superiority, non-inferiority and equivalence”* released for review September 1999):

Switching the objective of a trial from non-inferiority to superiority is feasible, provided:

- The trial has been properly designed and is of sufficiently high quality to provide a reliable assessment of non-inferiority.
- Exact p-values for superiority are presented to allow independent assessment of the strength of the evidence.
- Analysis according to the intention-to-treat principle is given greatest emphasis.

Switching the objective of a trial from superiority to non-inferiority may be feasible, provided:

- The non-inferiority margin with respect to the control regimen was pre-defined or can be justified.
- Analysis according to the intention-to-treat principle and per-protocol analysis give similar findings.
- The trial has been properly designed and is of sufficiently high quality to provide a reliable assessment of non-inferiority and is capable of detecting relevant differences if they exist.
- There is direct or indirect evidence that the control treatment is showing its usual level of efficacy.

While we appreciate the flexibility offered in the description of analyses that should be included in all NDAs, we believe that designating the analysis presented in the recent approved labels as preferred would be beneficial. It would add certainty and predictability to the development process, and it would serve to minimize the differences in analyses presented in the published literature and at public meetings. These differences have the unfortunate effect of confusing HIV treaters who need clear, intelligible information that can be readily compared across products.

Section IV. Traditional Approval

B. Efficacy

1. Study Design

The first paragraph states that “*the types of studies included may partly determine the indications granted*”. A hallmark of drug regulation in the US is that “what you study is what you get in labeling.” Therefore, the words “may partly” should be replaced with “will.”

2. Study Endpoints

1st Paragraph

We propose that the first sentence be changed to read as follows: “*The proportion of patients with HIV RNA levels below the assay limit at 48 weeks (or longer) and time-to-loss-of virologic-response **will** be considered primary endpoints for trials supporting traditional approval when based on evidence of durable suppression of viral replication.*”

The first paragraph also states that the investigational drug should show no deleterious effect on clinical endpoints and should show favorable CD4 responses. While this is generally true for therapy-naïve subjects, DAVDP is well aware that therapy-experienced or salvage patients may not necessarily demonstrate the same degree of response in relation to CD₄ cell counts as would be expected for therapy-naïve subjects. In addition, patients who already have high CD₄ cell counts (e.g., primary HIV infection) may not have a significant increase in CD₄ cell counts due to the “ceiling effect”.

4th Paragraph

FDA should acknowledge that neither the sponsor nor investigator will know, in every case, why an individual patient chose to stop participating in a study. Therefore, it will not be possible to determine the time until a dose-limiting adverse reaction in such cases. As you know, patients are entirely free to exit a study at any time, for any reason, and patients have no obligation to the investigator or sponsor or IRB to provide a specific reason for leaving the study. We propose that these subjects be considered as failures in the intent-to-treat analysis.

Proportion below the assay limit

This paragraph contains the sentence: “*The proportion of patients with HIV RNA levels below the assay limit at 48 weeks will usually be an important **secondary** endpoint in superiority trials.*” The preceding section on Study Endpoints contains this sentence: “*The proportion of patients with HIV RNA levels below the assay limit at 48 weeks (or longer) and time-to-loss-of-virologic-response may be **considered primary** endpoints.*” These two sentences appear to be in conflict. Please clarify.

Statistical methods for time-to-event analyses are described as insufficient for equivalence comparisons. While we agree that the summary statistics from the classic time-to-event analysis, i.e., the hazard ratio and its confidence interval, do not lend themselves to easy clinical interpretation, they nonetheless may be used to perform a non-inferiority comparison. This is discussed in detail in Chapter 11, The Design and Analysis of Equivalence Trials, AIDS Clinical Trials, ed. D. M. Finkelstein and D.A. Schoenfeld, Wiley-Liss, Inc. 1995.

Clinical Endpoints

This paragraph states that “*Adequate and well-controlled trials showing clinical benefit as measured by HIV-related clinical events and survival will continue to be considered necessary support for an application for traditional approval.*” This statement is inconsistent with DAVDP’s current practice of granting traditional approval based on trials that demonstrate sustained suppression of plasma HIV-1 RNA (in the absence of data on survival).

Instead, we propose the following statement: “*Sponsors are encouraged to discuss with the Division other innovative study designs that could be considered for traditional approval. These types of studies may include clinical endpoint studies such as vertical transmission studies and primary HIV infection trials.*”

C. Statistical Considerations

FDA requests that sponsors provide all available “extended data,” i.e., data beyond 48 weeks of therapy, in the application for traditional approval (when that application is based primarily on evidence of durable viral suppression through 48 weeks). We respectfully disagree with this request. By definition, this “extended data” will be an incomplete data set on only a portion of the patients. In fact, the proportion of patients with data will decrease at longer time points. Nonetheless, it is certainly tempting to make early, perhaps unfounded judgements based on these partial data sets. In our view, this temptation can best be avoided by not submitting the extended data until a later time when the data set is complete through the next pre-defined milestone time (e.g., 72 weeks). In our view, a sponsor’s proposal to reach conclusions based on a partial **dataset** is rarely acceptable to FDA; therefore, as a matter of consistency, FDA should not request a partial **dataset** from a sponsor to use in review and formulation of even preliminary conclusions on a sponsor’s applications.

Section V. Pharmacokinetic Considerations

We offer the below rewording of this entire section, which is intended to make it consistent with existing final and draft guidance documents pertaining to pharmacokinetic and pharmacodynamic considerations.

V. PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

In order to characterize drug disposition (absorption, distribution, metabolism, and excretion) and effect, pharmacokinetic and pharmacodynamic studies should be conducted as discussed in *General Considerations for the Clinical Evaluation of Drugs* (FDA 77-3040, February 1997) and in International Conference on Harmonisation (ICH) guidance *E4 Dose-Response Information to Support Drug Registration* (*Federal Register* 59:55972-55976, November 1994). Evaluations of population subgroups (e.g. age, gender, and ethnicity) should be conducted as appropriate to identify potential differences in drug safety and efficacy. The FDA guidance document on *Population Pharmacokinetics* (February 1999) supports the use of population **pharmacokinetic/pharmacodynamic** approaches to examine subgroups. Additional reference is made to this topic in other FDA guidance documents, including *General Considerations for the Clinical Evaluation of Drugs* (February 1997), *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products* (draft guidance *Federal Register* 63:65794-65795, November 1998), *Study of Drugs Likely to be Used in the Elderly* (August 1989) and *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* (July 1993); and in International Conference on Harmonisation (ICH) guidances, including *E4 Dose-Response Information to Support Drug Registration* and *E7 Studies in Support of Special Populations: Geriatrics* (August 1994). Additionally, sponsors should become familiar with three related regulatory documents pertaining to

pediatric patients: (1) the final rule on the pediatric subsection of labeling, including the principles of applying evidence of efficacy from studies in adults to the pediatric population (Federal Register 59:64240-64250, December 13, 1994) (2) the pediatric rule, "*Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biologic Products in Pediatric Patients*," (Federal Register 63:66632-66672, December 2, 1998); and (3) pediatric exclusivity provision of FDAMA, whereby submission of pediatric data responsive to a formal Written Request from FDA can qualify a product for additional marketing exclusivity as permitted in section 505A of the Federal, Food, Drug, and Cosmetic Act (21 U.S.C. 355a).

Currently, the recommended treatment of HIV- 1 infection involves use of various antiretroviral drugs in combinations. Also, treatment of HIV- 1 infected patients may require combination drug therapy for treatment or prophylaxis of opportunistic infections (e.g., *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex, tuberculosis, fungal infections) or other co-morbid conditions (e.g., depression, diabetes, elevated cholesterol). Consequently, drug-drug interaction studies to examine the potential impact on safety and efficacy should be conducted as guided by knowledge of drug metabolism and disposition and by the therapeutic range of the coadministered agents. Reference is made to this subject in other FDA guidance documents, including *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro* (April 1997) and *In Vivo Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling* (Draft Guidance, Federal Register 63:64269-64270, November 1998) and *CPMP Note for Guidance on the Investigation of Drug Interactions* (December 1997). Drug-drug interaction studies should be conducted as necessary and appropriate for the development of the compound (in view of the pharmacokinetic properties of the drug) and to yield appropriate information for inclusion in professional labeling.

Section VI. HIV RNA Assays

It would be helpful if a list of the approved assays was included either at the beginning of this section or published on the FDA web page so that this information is readily publicly accessible.

The 3rd paragraph to the end of the section applies to investigational assays. To clarify this point, we suggest that this section be labeled INVESTIGATIONAL HIV RNA ASSAYS.

HIV Resistance

At the conclusion of the November 2-3, 1999 Antiviral Drugs Advisory Committee meeting, Dr. Scott Hammer summarized the discussions on resistant HIV-1 and the potential role for assays of viral resistance in antiretroviral drug development. It was concluded that resistance

testing does have a major role in drug development. Both genotyping and phenotyping are important tools in the development process for drugs to treat HIV infection. No single assay was recommended, but the sponsor should select the assay that is best suited to the objectives of the study.

Expectations are that future New Drug Applications would contain data on the following:

- Validation data on resistance assays used in sponsored trials.
- Passage of viruses in the presence of drug with genotypic and phenotypic characterization of emerging mutants. The significance of the mutations should be tested by site-directed mutagenesis.
- Testing of the drug against a panel of well-characterized HIV isolates with known mutations and susceptibility profiles.
- Phenotypic and genotypic characterization of mutants from patients with virologic failure. These mutants can be compared with the baseline isolates for phenotype and genotype.
- Information on potential confounding factors (pharmacokinetic factors, drug-drug interactions and adherence).

It would be helpful to know if the DAVDP shares the Committee's view on the role of resistance testing and if this reflects FDA's expectations for future drug development programs.

Thank you for the opportunity to provide comments on this important guidance document. We hope you find these comments constructive.

Sincerely,



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